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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,495	11/20/2003	Theresa L. O'Keefe	3258.1009-001	9229

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,495	O'KEEFE, THERESA L.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16,20-22,24-29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16,20-22,24-29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 8/14/06, is acknowledged.

2. Claims 15-16, 20-22, 24-29 and 31-33 are pending and under examination.

3. Applicant's IDS filed, 5/18/06, is acknowledged, however, references A5, A6 and C18 are crossed out because they are duplicates of references A, B and X, respectively, listed on the PTO FORM 892, mailed 5/10/06.

4. The following new ground of rejections are necessitated by the amendment submitted 8/14/06.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-16, 20-22, 24-29 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide **enablement** for a method of treating any "condition in a patient characterized by activation of an inflammatory cytokine cascade", comprising administering to the patient an effective amount of a polypeptide comprising any high mobility group box protein (HMGB) a box which can inhibit release of a proinflammatory cytokine from any "cell", wherein said HMGB A box is any "HMG1L5 A box" in claim 15, or any "condition in a patient characterized by activation of an inflammatory cytokine cascade", comprising administering to the patient an effective amount of a polypeptide , wherein said polypeptide is any high mobility group box protein (HMGB) a box which can inhibit release of a proinflammatory cytokine from any "cell", wherein said HMGB A box is any "HMG1L5 A box" in claim 16, wherein the condition is sepsis in claims 20 and 27, rheumatoid arthritis in claims 21 and 28 or endotoxic shock or allograft in claims 22 and 29, the methods further comprising administering an antagonist of an early sepsis mediator in claims 25 and 32, wherein the antagonist is an antagonist of TNF in claims 26 and 33. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 5/10/06.

Applicant's arguments, filed 8/14/06, have been fully considered, but have not been found convincing.

Applicants submit that they are not required to demonstrate their claimed method would work on each and every disease imaginable, but rather provide enablement for a representative number of species. Representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation. The Applicant has shown that HMGB 1 A Box protein successfully treats mice during sepsis. (Specification, Example 12, page 63). The specification further teaches that sepsis is one of several conditions characterized by activation of an inflammatory cytokine cascade. (Specification, pages 30-32).

Contrary to applicant submission, Example 12, on page 63 is not representative of the claimed method of treating any condition in a patient characterized by activation of an inflammatory cytokine cascade with the claimed HMG1L5 A box polypeptide. Example 12, uses passive immunization of an anti-HMGB1 antibody, while the instant method uses an active immunization with the claimed HMG1L5 A box polypeptide.

Applicant further argues that it is well-settled law that the enablement and utility requirements of the patent law do not impose on applicants for patents the burden of proving clinical safety and efficacy (see, e.g., M.P.E.P. §§ 2107.01(III-IV), p. 2100-34-37 and 2107.3(V), p. 2100-45-46 (8th Ed., 3rd Rev., August 2005). Therefore, the applicant has no duty to provide in vivo data in humans to show that the claimed method would work.

While testing for the full safety and effectiveness of the HMGL5 A box is more properly left to the Food and Drug Administration (FDA), Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate data obtained from the mice passively immunized with anti-HMGB1 antibody and the effects of the antibody (anti-HMGB1 antibody) treatment on the septic mice to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention using an active immunization with an HMG1L5 A box polypeptide.

With respect to Friend et al. (Transplantation, 68:1625-1631 (1999); Applicant contends that the assertion was not taught by Friend, but was provided as a commentary by Wood and Pockley on the research reported elsewhere in the journal by Friend. The commentators assert that the clinical application of monoclonal antibodies is restricted by the development of a humoral immune reaction to the mouse or rat immunoglobulin protein, but the research by Friend in this same journal issue reports a Phase I study of an antibody in renal transplant recipients. Indeed, Friend provided evidence of improvements in renal function and biopsy appearances in the majority of the treated patients. Even the commentators agreed that "[t]he generation of engineered antibodies that are capable of treating/reversing graft rejection without concomitant toxicity is exciting." (last paragraph, page 1625). Therefore, in contrast to assertion of disappointment made by the Examiner, this reference demonstrates the positive impact that humanized antibodies can have in the clinic.

The Examiner thanks Applicant for pointing that the teachings came from Wood and Rockley instead of Friend et al. However, the issue is not the humanized antibody, rather whether the

specification is enabled for a method of treating any condition in a patient characterized by activation of an inflammatory cytokine cascade, including renal transplantation. Wood and Rockley teach (see page 1625, 1st col., ¶1) that in clinical transplantation the impact of the mAbs on therapeutic regimens has been rather disappointing. Wood and Pockley teach this is in stark contrast to experimental transplantation where a number of protocols have shown that mAbs can induce indefinite graft survival in rodent models (see page 1625, 1st col., ¶1). While the commentators teach that "[t]he generation of engineered antibodies that are capable of treating/reversing graft rejection without concomitant toxicity is exciting." (last paragraph, page 1625), they further teach that it remains to be seen how the clinical efficacy of humanized anti-CD3 mAb reagent will compare to that of daclizumab (see page 1626, last ¶).

With respect to Toogood et al. (Transplantation, 62:851-855 (1996) teachings. Applicant contends that it is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Applicant concludes that enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id. Therefore, despite the fact that there may be different mechanisms of rejection between the gut wall compartment of a small bowel transplant and other vascularized allografts, Applicant is claiming a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade. The activation of an inflammatory cytokine cascade is not necessarily different when different mechanisms of rejection are involved in different organ transplantations. Thus, only routine experimentation by one skilled in the art is required to practice the invention as claimed. As the specification teaches, "[t]he route of administration and the dosage of the composition to be administered can be determined by the skilled artisan, without undue experimentation, in conjunction with standard dose-response studies." (Specification, page 32).

However, while Applicant argues that the activation of an inflammatory cytokine cascade is not necessarily different when different mechanisms of rejection are involved in different organ transplantations, however, the arguments of counsel cannot take the place of objective evidence in the record (see Krenger and Ferrara teachings, for example). In re Schulze , 145 USPQ 716, 718 (CCPA 1965). The Examiner directs Applicant's attention to Krenger and Ferrara who teach that a classical lethal acute GVHD is linked to the preferential activation of donor T cells secreting Il-2 and IFN-γ which the less severe chronic form of GVHD is characterized a type 2 cytokine response where IL-4 and IL-10 are preferentially produced after BMT (see page 61, 2nd col., lines 38-43 and page 62, lines 1-10).

With respect to Freeman et al teachings, Applicant argues that based on their detailed analysis of a large number of studies, Freeman concludes that the use of mediator-specific antagonists "in humans with sepsis actually does produce a small beneficial effect on survival .... (i.e., approximately a 7-8% decrease in mortality)" (Freeman, page 974, first paragraph). Moreover, Freeman offers a possible explanation for the observed discrepancy between the beneficial

effects in animal studies and human clinical trials, namely that the variables that potentially alter the effects of anti-inflammatory agents (e.g., type and site of bacterial infection, timing of administration of anti-inflammatory therapy, and the use of supportive measures) were not thoroughly evaluated in animal models (Freeman, page 973, section entitled "Were Animal Models Predictive of the Effects of Anti-Inflammatory Agents in Humans").

However, if the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied. "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements...However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims." MPEP § 2164.03. "Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein." Ex parte Maas, 9 USPQ2d 1746. Given Freeman et al estimate that anti-inflammatory agents reduce mortality by approximately 7-10% in the pathogenesis of sepsis "beneficial effect is small", the specification neither discloses working example of HMG1L5 A box in the treatment of sepsis nor does it exemplify any in vivo empirical data relevance to the claimed human efficacy to predict the efficacy of the claimed HMG1L5 A box. The lack of any working examples is exacerbated because the invention is in a highly unpredictable art (see Freeman et al)-prevention or treatment of sepsis - and while the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying proinflammatory cytokines and physiologic bases of the therapeutic effects of any HMG1L5 A box in the prevention or treatment of sepsis.

With respect to the full-length polypeptide of an HMG1L5 issue, Applicant disagrees. Applicant asserts that the claim does not read on full length HMGB because the claim recites functional limitations that the polypeptide "can inhibit release of a proinflammatory cytokine from a cell." Thus, the claim does not read on any polypeptide which stimulates proinflammatory cytokine release.

However, the specification appears to recognize that the wild-type HMGB1 significantly *stimulated* TNF release by monocytes cultures. Thus, faced with contradictory and seemingly mutually exclusive function regarding the activity of the a polypeptide "comprising an HMG1L5 A box" that *inhibit* the release of a proinflammatory cytokine form a cell, undue experimentation would be required of the skilled artisan to determine the effect of the claimed polypeptide, for example, on the release of a proinflammatory cytokine from a cell. Further, absent a positive correlation between a polypeptide comprising an HMG1L5 A box and a condition characterized by activation of an inflammatory cytokine cascade, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue. In addition, absent the ability to predict which of these polypeptides would function as claimed, for

one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Regarding the issue that the claimed HMGB1 related sequences are encoded by pseudogenes or very similar genes. Further the issue that the specification fails to show that those non-functional polypeptides encoded by the pseudogenes represent a functional HMGB A box that would inhibit release of a proinflammatory cytokine from any cell. And the issue *In vitro* and animal model studies have not correlated well with in vivo clinical trial results in patients. Applicant contends that he has no duty to provide in vivo clinical data to show that the claimed method would work, or to prove a certain level of efficacy. It is well within the expectations of one skilled in the art that they would need to perform a certain amount of experimentation to determine the efficacy of the claimed method in a patient. Routine experimentation is expected, as the amount needed will vary based on, for example, the patients and severity of the conditions to be treated.

However, there must be a rigorous correlation of pharmacological activity between the disclosed in vitro utility and an in vivo utility to establish practical utility. In the instant case the claimed HMGB1 related sequences, such as HMG1L5 A box, lack any such correlation because the specification fails to show that the claimed HMG1L5 A box have an *in vitro* nor an *in vivo* activity. The instant claims are drawn to a large genus of methods which have not been developed yet to the point where a specific benefit exists in currently available form. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Regarding the issue of an antagonist of an early sepsis mediator. Applicant points to the specification on page 34, lines 9-12. Applicant points that the specification discloses nonlimiting examples including TNF, IL-1α, IL-1β, IL-6, PAF and MIF. However, those examples are the cytokines not the claimed antagonists of an early sepsis mediator.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

8. Claims 15-16, 20-22, 24-29 and 31-33 are rejected under 35 U.S.C. 102(e) as being anticipated by WO200292004-A2.

The `004 publication teaches and claims a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to the patient a polypeptide comprising a vertebrate high mobility group protein (HMG) A box or a non-naturally occurring HMG A box (such as claimed HMG1L5, see published SEQ ID NO:18, page 37 and page 32, lines 8-27 in particular) which can inhibit release of a proinflammatory cytokine from a vertebrate cell treated with high mobility group (HMG) protein in an amount sufficient to inhibit release of the proinflammatory cytokine from the cell (see published claims 15-16 in particular). The `004 publication further teaches that a composition comprising any of the polypeptides can inhibit a condition characterized by activation of an inflammatory cytokine cascade. The condition can be one where the inflammatory cytokine cascade causes a systemic reaction, such as with endotoxic shock, rheumatoid arthritis, allograft rejection or sepsis (see page 32, lines 8-28 and Example 12 in particular). Also, the `004 publication teaches that the composition can further comprise an antagonist of an early sepsis mediator. The antagonist of an early sepsis mediator is preferably an antagonist of a cytokine selected from the group consisting of TNF, IL-1.alpha., IL-1.beta., MIF and IL-6, more preferably, an antibody to TNF or MIF, or an IL-1 receptor antagonist (see page 4, line 24 to page 5, line 2 in particular).

The reference teachings anticipate the claimed invention.

9. Claims 15-16, 20-22, 24-29 and 31-33 stand rejected under 35 U.S.C. 102(e1) as being anticipated by US/2003/0060410 A1 for the same reason set forth in the previous Office Action mailed 5/10/06.

Applicant's arguments, filed 8/14/06, have been fully considered, but have not been found convincing.

Applicant argues that the `410 publication does not teach each and every aspect of Applicant's claimed invention. In particular, the specific HMGB A box homolog claimed in the present application is not disclosed in the `410 application.

Contrary to applicant assertion the `410 publication teaches the particular HMG1L5 A box (see published SEQ ID NO: 18 in particular).

10. Claims 15-16, 20-22, 24-29 and 31-33 stand rejected under 35 U.S.C. 102(e1) as being anticipated by US/2003/0144201 A1 for the same reason set forth in the previous Office Action mailed 5/10/06.

Applicant's arguments, filed 8/14/06, have been fully considered, but have not been found convincing.

Applicant argues that the `201 publication does not teach each and every aspect of Applicant's claimed invention. In particular, the specific HMGB A box homolog claimed in the present application is not disclosed in the `201 application.

Contrary to applicant assertion the `201 publication teaches the particular HMG1L5 A box (see published SEQ ID NO: 18 in particular).

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 9, 2007

Maher Haddad

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